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[Intervention Review]

Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care

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ABSTRACT

Background

Opioid-induced bowel dysfunction (OIBD) is characterised by constipation, incomplete evacuation, bloating, and gastric reflux. It is one of the major adverse events of treatment for pain in cancer and in palliative care, resulting in increased morbidity and reduced quality of life.

This is an update of two Cochrane reviews. One was published in 2011, Issue 1 on laxatives and methylnaltrexone for the management of constipation in people receiving palliative care; this was updated in 2015 and excluded methylnaltrexone. The other was published in 2008, Issue 4 on mu-opioid antagonists (MOA) for OIBD. In this updated review, we only included trials on MOA (including methylnaltrexone) for OIBD in people with cancer and people receiving palliative care.

Objectives

To assess the effectiveness and safety of MOA for OIBD in people with cancer and people receiving palliative care.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, and Web of Science to August 2017. We also searched clinical trial registries and regulatory websites. We contacted manufacturers of MOA to identify further data.

Selection criteria

We included randomised controlled trials (RCTs) that assessed the effectiveness and safety of MOA for OIBD in people with cancer and people at a palliative stage irrespective of the type of terminal disease they experienced.

Data collection and analysis

Two review authors assessed risk of bias and extracted data. The appropriateness of combining data from the trials depended upon sufficient homogeneity across the trials. Our primary outcomes were laxation, impact on pain relief, and adverse events. Impact on pain relief was a primary outcome because a possible adverse effect of MOAs is a reduction in pain relief from opioids. We assessed the evidence on these outcomes using GRADE.

Main results

We identified four new trials for this update, bringing the total number included in this review to eight. In total, 1022 men and women with cancer irrespective of stage or at a palliative care stage of any disease were randomised across the trials. The MOAs evaluated were oral naldemedine and naloxone (alone or in combination with oxycodone), and subcutaneous methylnaltrexone. The trials compared with MOA with a placebo or with the active intervention administered at different doses or in combination with other drugs. The trial of naldemedine and the two of naloxone in combination with oxycodone were in people with cancer irrespective of disease stage. The trial on naloxone alone was in people with advanced cancer. The four trials on methylnaltrexone were undertaken in palliative care where most participants had cancer. All trials were vulnerable to biases; four were at a high risk as they involved a sample of fewer than 50 participants per arm.

In the trial of naldemedine compared to placebo in 225 participants, there were more spontaneous laxations over the two-week treatment for the intervention group (risk ratio (RR) 1.93, 95% confidence intervals (CI) 1.36 to 2.74; moderate-quality evidence). In comparison with higher doses, lower doses resulted in fewer spontaneous laxations (0.1 mg versus 0.2 mg: RR 0.73, 95% CI 0.55 to 0.95; 0.1 mg versus 0.4 mg: RR 0.69, 95% CI 0.53 to 0.89; moderate-quality evidence). There was moderate-quality evidence that naldemedine had no effect on opiate withdrawal. There were five serious adverse events. All were in people taking naldemedine (low-quality evidence). There was an increase in the occurrence of other (non-serious) adverse events in the naldemedine groups (RR 1.36, 95% CI 1.04 to 1.79, moderate-quality evidence). The most common adverse event was diarrhoea.

The trials on naloxone taken either on its own, or in combination with oxycodone (an opioid) compared to oxycodone only did not evaluate laxation response over the first two weeks of administration. There was very low-quality evidence that naloxone alone, and moderate-quality evidence that oxycodone/naloxone, had no effect on analgesia. There was low-quality evidence that oxycodone/naloxone did not increase the risk of serious adverse events and moderate-quality evidence that it did not increase risk of adverse events.

In combined analysis of two trials of 287 participants, we found methylnaltrexone compared to placebo induced more laxations within 24 hours (RR 2.77, 95% CI 1.91 to 4.04. I^2 = 0%; moderate-quality evidence). In combined analysis, we found methylnaltrexone induced more laxation responses over two weeks (RR 9.98, 95% CI 4.96 to 20.09. I^2 = 0%; moderate-quality evidence). The proportion of participants who had a rescue-free laxation response within 24 hours of the first dose was 59.1% in the methylnaltrexone arms and 19.1% in the placebo arm. There was moderate-quality evidence that the rate of opioid withdrawal was not affected. Methylnaltrexone did not increase the likelihood of a serious adverse event; there were fewer in the intervention arm (RR 0.59, 95% CI 0.38 to 0.93; I^2 = 0%; moderate-quality evidence). There was no difference in the proportion of participants experiencing an adverse event (RR 1.17, 95% CI 0.94 to 1.45; I^2 = 74%; low-quality evidence). Methylnaltrexone increased the likelihood of abdominal pain and flatulence.

Two trials compared differing methylnaltrexone schedules of higher doses with lower doses. For early laxation, there was low-quality evidence of no clear difference between doses on analgesia and adverse events. Both trials measured laxation response within 24 hours of first dose (trial one: RR 0.82, 95% CI 0.41 to 1.66; trial two: RR 1.07, 95% CI 0.81 to 1.42).

Authors' conclusions

In this update, the conclusions for naldemedine are new. There is moderate-quality evidence to suggest that, taken orally, naldemedine improves bowel function over two weeks in people with cancer and OIBD but increases the risk of adverse events. The conclusions on naloxone and methylnaltrexone have not changed. The trials on naloxone did not assess laxation at 24 hours or over two weeks. There is moderate-quality evidence that methylnaltrexone improves bowel function in people receiving palliative care in the short term and over two weeks, and low-quality evidence that it does not increase adverse events. There is a need for more trials including more evaluation of adverse events. None of the current trials evaluated effects in children.

PLAIN LANGUAGE SUMMARY

Mu-opioid antagonists for bowel dysfunction due to opioids in people with cancer and people receiving palliative care

Background

Opioids (morphine-like drugs) are used to treat severe pain. Unfortunately, they cause side effects. Opioid-induced bowel dysfunction (OIBD) is a term used to describe constipation, incomplete evacuation of the bowels, bloating, and increased reflux (flowing back) of stomach contents. OIBD may be so severe that a person chooses to limit opioid treatment to improve bowel function. OIBD is common in people with cancer and people receiving palliative care (care given to people with a terminal illness when a cure is no longer possible). Laxatives are often the first-choice treatment for OIBD. They may not always work. Mu-opioid antagonists (MOA) are specific medicines for OIBD. Clinical guidelines may recommend them when laxatives fail.

Trial characteristics

The aim of this updated review was to determine what we know about the effectiveness and safety of MOA for the management of OIBD in people with cancer and people receiving palliative care and for whom laxatives have failed. A possible side effect of an MOA is reduced pain relief from opioids; therefore, we looked at its impact on pain relief. We only included randomised controlled trials (RCTs), which are well-designed clinical trials that provide the most reliable evidence. RCTs needed to evaluate an MOA, such as the medicines naldemedine,

methylnaltrexone, and naloxone. The trial comparison groups could be a placebo (a substance with no known active effect), usual care, or another treatment such as a different type of MOA.

Key results

Our search to August 2017 found eight trials involving 1022 adults. The MOAs evaluated in people with cancer were oral naldemedine and naloxone taken in combination with an opioid treatment (for pain). Methylnaltrexone given by injection was evaluated in palliative care where most participants had advanced cancer.

The results were naldemedine or methylnaltrexone compared with placebo. For naloxone, they were either in comparison with a placebo or with opioid treatment only.

We rated the quality of the evidence from studies as very low to moderate. Very low means that we are very uncertain about the results. High means that we are very confident in the results. There were problems with the design of studies, including under-reporting of trial methods.

Bowel movements within 24 hours and up to two weeks

There was moderate-quality evidence that naldemedine increased bowel movements up to two weeks. Trials did not measure the effects of naloxone on bowel movements at two weeks. Methylnaltrexone increased bowel movements or laxations (softer stools) within 24 hours and up to two weeks (moderate-quality evidence).

Pain relief

There was moderate-quality evidence that naldemedine did not change pain relief. Trials did not measure pain intensity with naldemedine. There was very low-quality evidence that naloxone taken on its own did not change pain relief. There was moderate-quality evidence that naloxone taken with an opioid treatment did not change pain relief. There was moderate- to low-quality evidence that methylnaltrexone did not change pain relief.

Risk of serious side effects (hospitalisation, life-threatening, or fatal) and other side effects

There was low-quality evidence that naldemedine and naloxone in combination with an opioid treatment did not increase the risk of serious side effects. For naldemedine, there were five serious side effects in the trial, although none were described as relating to the study drug. Methylnaltrexone probably did not increase the risk of serious side effects (moderate-quality evidence).

There was moderate-quality evidence that naldemedine increased the risk of side effects. There was moderate-quality evidence that naloxone taken with oxycodone (an opioid painkiller) did not increase the risk of side effects. There was low-quality evidence that methylnaltrexone did not increase the overall risk of a side effect. Methylnaltrexone increased the risk of abdominal pain and flatulence.

Conclusion

There was moderate-quality evidence to suggest that naldemedine improved bowel function over two weeks in adults with cancer and OIBD but increased the risk of side effects; and that methylnaltrexone improved bowel function in people receiving palliative care and low-quality evidence that methylnaltrexone did not increase side effects. The results of this review need to be interpreted with caution as they were not obtained from high-quality evidence. There were no studies in children.